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Methylenespiro[2.3]hexanes via Nickel-Catalyzed Cyclopropanations with [1.1.1]Propellane

Songjie Yu, Adam Noble, Robin B. Bedford,* and Varinder K. Aggarwal*

School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, U.K.

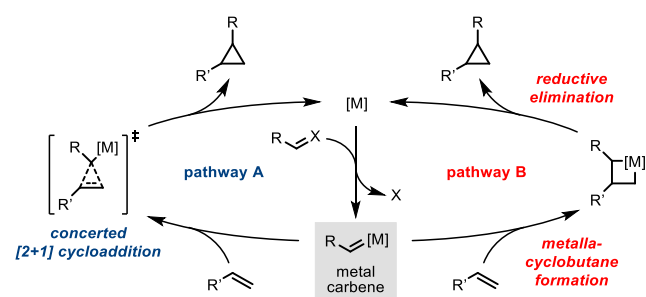
Supporting Information Placeholder

ABSTRACT: [1.1.1]Propellane is a highly strained tricyclic hydrocarbon whose reactivity is dominated by addition reactions across the central inverted bond to provide bicyclo[1.1.1]pentane derivatives. These reactions proceed under both radical and two-electron pathways, hence providing access to a diverse array of products. Conversely, transition metal-catalyzed reactions of [1.1.1]propellane are underdeveloped and lack synthetic utility, with reported examples generally yielding mixtures of ring-opened structural isomers, dimers, and trimers, often with poor selectivity. Herein, we report that nickel(0) catalysis enables the use of [1.1.1]propellane as a carbene precursor in cyclopropanations of a range of functionalized alkenes to give methylenespiro[2.3]hexane products. Computational studies provide support for initial formation of a Ni(0)-[1.1.1]propellane complex followed by concerted double C–C bond activation to give the key 3-methylenecyclobutylidene-nickel intermediate.

1. Introduction

Catalytic cyclopropanation is a powerful method for generating three-membered carbocycles from alkenes and appropriate carbene precursors.¹ Key to the catalytic process is the formation of a transition metal carbene intermediate (Scheme 1), which then reacts with an alkene in either a concerted manner (pathway A),^{2,3} wherein the alkene attacks the carbene moiety directly to form two C–C bonds simultaneously, or in a stepwise fashion via the formation of a metallacyclobutane intermediate (pathway B).^{4–6} Irrespective of the pathway adopted, the formation of a carbene complex is regarded as pivotal to the transformation. Typically, this is accomplished by taking advantage of highly reactive compounds, such as diazoalkanes,⁷ containing weak C–X bonds that are easily cleaved by the metal catalyst.⁸

Scheme 1. Generalized mechanisms for catalytic alkene cyclopropanation with a metal carbene complex



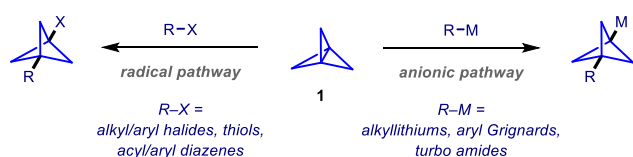
A less common approach to metal carbenes is via C–C bond activation,⁹ which is challenging due to the inertness of C–C

bonds and their lack of interaction with transition metal catalysts. Typically, catalytic C–C bond activation protocols require the use of directing groups¹⁰ or activated strained ring systems, including cyclopropanes^{11,12} or cyclobutanones,¹³ and proceed via cleavage of a single C–C bond to generate a metallacycle intermediate. Conversely, access to metal carbene complexes requires a double C–C bond activation of cyclopropanes, via a formal retro-cyclopropanation. While the use of simple cyclopropanes as carbene precursors is rare,¹⁴ systems that impart additional ring-strain as a crucial driving force have been exploited to promote the challenging double C–C bond activation.^{15,16} For example, bicyclo[1.1.0]butanes have been employed as metal carbene precursors under rhodium¹⁷ and nickel catalysis.¹⁸ In contrast, [1.1.1]propellane,¹⁹ which is considerably more strained than bicyclo[1.1.1]butane, has found little application as a metal carbene precursor.

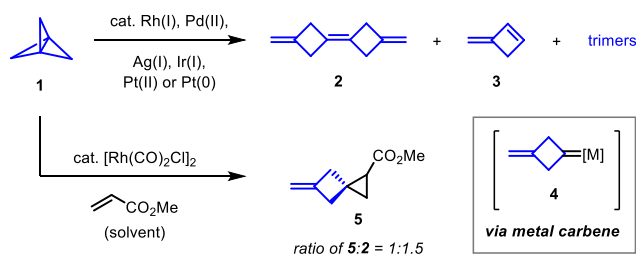
[1.1.1]Propellane (**1**) is a highly strained tricyclic hydrocarbon, with a calculated strain energy of between 98 and 113 kcal/mol.²⁰ This is attributed to the unusual ‘inverted’ central σ -bond between its bridgehead carbons. As a result, the reactivity of **1** has been dominated by strain-release, wherein additions across the bridgehead bond yield bicyclo[1.1.1]pentane derivatives either via single-electron²¹ or two-electron pathways (Scheme 2a).^{22,23} Despite the growing number of synthetic methods for accessing functionalized bicyclo[1.1.1]pentanes from **1**, reports of transition metal-catalyzed reactions of **1** are rare. However, its high ring-strain should provide the required driving force to facilitate metal-catalyzed retro-cyclopropanation, in which double C–C bond activation furnishes a metal carbene species.

Scheme 2. Transformations of [1.1.1]propellane

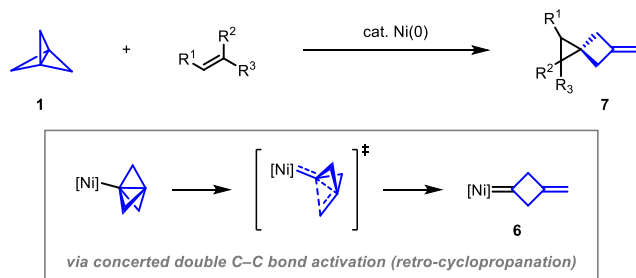
(a) Bicyclo[1.1.1]pentane formation for [1.1.1]propellane (well-established)



(b) Transition metal-catalyzed reactions of [1.1.1]propellane (rare)



(c) Nickel-catalyzed cyclopropanations with [1.1.1]propellane (this work)



To date, the limited reports of carbene formation from **1** have resulted in mixtures of isomerization and oligomerization products, thus lacking synthetic utility. Thermal ring-opening of **1** under flow conditions at 430 °C yields 1,2-dimethylenecyclopropane,²⁴ a reaction subsequently shown to occur via a free carbene intermediate (methylenecyclobutylidene) with an activation energy of 39.6 kcal/mol.²⁵ Wiberg explored ring-opening reactions of **1** in the presence of various transition metal catalysts (Scheme 2b).²⁶ With Rh(I) or Pd(II) an almost instantaneous reaction occurred to give the ring-opened dimer **2**, whereas Ag(I), Ir(I), Pt(II), and Pt(0) led to slower reactions to produce varying amounts of dimer **2**, methylene cyclobutene (**3**), and various trimeric products. The authors proposed that these were formed via metal carbene intermediates **4**. This was supported by a cyclopropanation reaction with methyl acrylate catalyzed by $[\text{Rh}(\text{CO})_2\text{Cl}]_2$, which gave methylenespiro[2.3]hexane **5** as a 1:1.5 mixture with **2**. However, formation of **5** required the use of methyl acrylate as the solvent, presumably to make cyclopropanation competitive with the rapid dimerization of the carbene intermediate.

We envisaged that the carbenes generated by metal-mediated ring-opening of **1** could be exploited more generally in cyclopropanation reactions with alkenes. Key to achieving this would be to suppress undesired isomerization and oligomerization reactions of the metal carbene intermediate. Herein, we report that nickel catalysis efficiently promotes cyclopropanation reactions of alkenes using **1** as a carbene

precursor (Scheme 2c). The reaction proceeds via double C–C bond activation of **1** to generate nickel carbene **6** and provides access to methylenespiro[2.3]hexanes **7** through cyclopropanation of a broad array of alkenes. Density functional theory (DFT) calculations provide insight into the key interaction between **1** and the Ni(0) catalyst and support the formation of the proposed 3-methylenecyclobutylidene nickel complex **6**.

2. Results and Discussion

Initial investigations focused on cyclopropanation of 4-vinylbiphenyl (**8a**) with **1** in the presence of various transition metal catalysts (Table 1). In line with the report by Wiberg,²⁶ a Rh(I) catalyst resulted in rapid formation of the dimerization product bis(3-methylenecyclobutylidene) (**2**) with no observable cyclopropanation (entry 1). Similarly, Ir(I), Pd(0), and Cu(I) catalysts failed to promote cyclopropanation (entries 2–4). Pleasingly, switching to $\text{Ni}(\text{cod})_2$ as the catalyst with the *N*-heterocyclic carbene (NHC) ligand SIMes (generated *in situ* from 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride [SIMes·HCl] and NaO'Bu) suppressed the dimerization pathway and resulted in formation of methylenespiro[2.3]hexane derivative **7a** in 64% yield after 20 h at 50 °C (entry 5).²⁷ Further evaluation of the

Table 1. Optimization studies^a

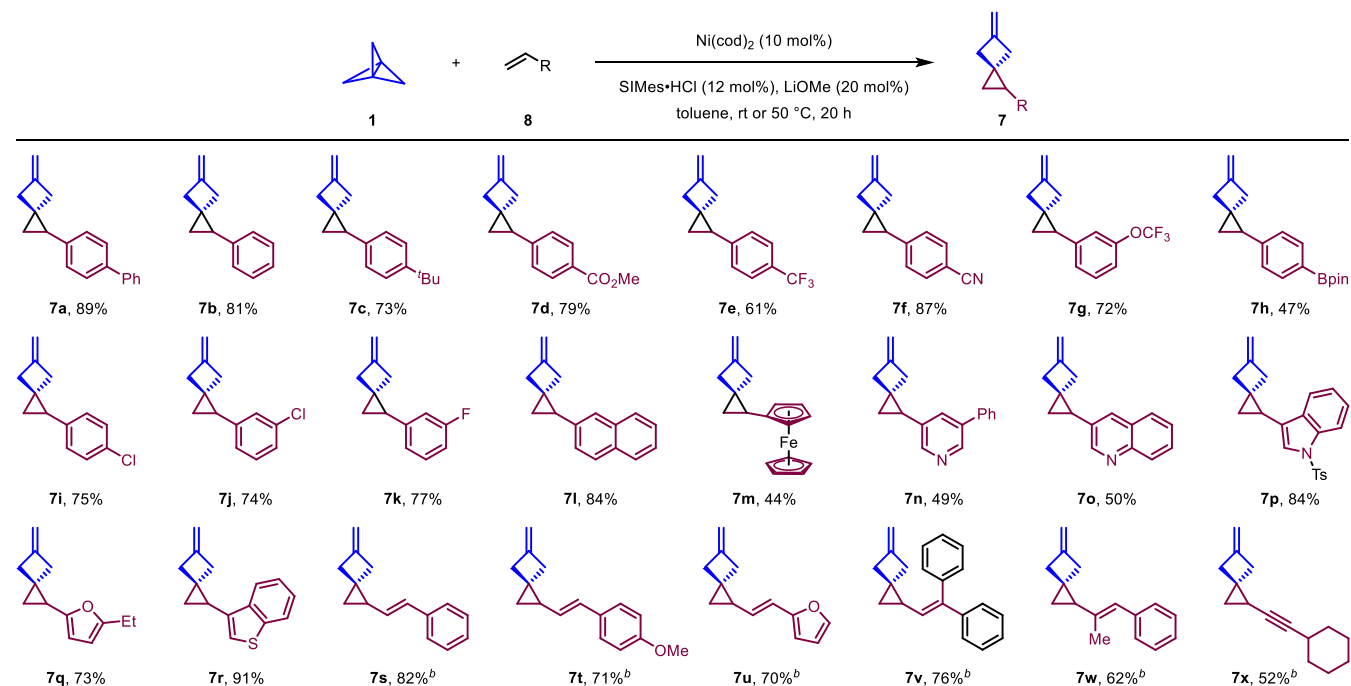
entry	catalyst (mol%)	x (mol%)	base	3 (%) ^b
1	Rh(cod) ₂ Cl (5)	-	-	0
2	Ir(cod) ₂ Cl (5)	-	-	0
3	Pd(dba) ₃ (5)	-	-	0
4	Cu(MeCN) ₄ PF ₆ (10)	- ^c	-	0
5	Ni(cod) ₂ (10)	12	NaO'Bu	64
6	Ni(cod) ₂ (10)	12	LiOMe	81
7	Ni(cod) ₂ (10)	12	LiO'Bu	67
8	Ni(cod) ₂ (10)	12	KO'Bu	69
9	Ni(cod) ₂ (10)	20	LiOMe	87 (76)
10	Ni(cod) ₂ (10)	12	LiOMe	(89) ^d
11	Ni(cod) ₂ (10)	12	LiOMe	(65) ^{d,e}
12	Ni(cod) ₂ (10)	-	-	(75) ^d
13	-	12	LiOMe	0

^a Reaction conditions: **8a** (0.20 mmol), **1** (0.7–0.9 M in Et₂O, 0.40 mmol), catalyst (5–10 mol%), SIMes·HCl (0–20 mol%), base (20 mol%), and solvent (3 mL) at 50 °C for 20 h. ^b Yields were determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. Numbers in parenthesis are isolated yields of the purified product. ^c 2,2-Bis((4*S*)-4-isopropylloxazoline)propane (12 mol%) was used as the ligand. ^d With 4.0 equiv **1**. ^e Using IMes·HCl (12 mol%) in place of SIMes·HCl.

base used to generate the NHC ligand revealed LiOMe to be optimal, affording **7a** in 81% yield (entries 6–8). Using a higher ligand loading of 20 mol% resulted in marginal increase in yield (entry 9). However, a significant improvement was observed upon increasing the amount of **1** from 2 equiv to 4 equiv, which allowed isolation of **7a** in 89% (entry 10). Changing the NHC ligand to 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes) resulted in a slightly decreased yield (entry 11). Interestingly, Ni(cod)₂ in the absence of NHC ligand was still an effective catalyst for cyclopropanation, providing **7a** in a slightly reduced yield of 75% (entry 12). Finally, a control experiment demonstrated the importance of the Ni(0) catalyst as no product was observed in its absence (entry 13), which is in line with the high energy barrier to free carbene formation via thermal rearrangement of **1**.²⁵

With optimal conditions for the nickel-catalyzed cyclopropanation established, the scope of the reaction was assessed (Scheme 3). A wide range of styrene derivatives reacted efficiently to provide cyclopropanes **7a–7k** in 47–89% yield, including those bearing electron-donating (**7c**) and electron-withdrawing substituents (**7d–7g**). It is notable that several reactive functional groups, including a pinacol boronic ester (**7h**), chloride (**7i** and **7j**), and fluoride (**7k**), are tolerated under the reaction conditions, despite them being known to undergo nickel-catalyzed transformations.²⁸ Alkenes substituted with electron-rich aromatic groups, such as naphthyl and ferrocenyl gave the spirocyclic products **7l** and **7m** in 84% and 44% yield, respectively. Heteroaromatic moieties are ubiquitous in bioactive molecules but their functionalization can be challenging using transition metal catalysis due to the potentially strong ligation to metal centers. In this catalytic system, a broad range of heteroaryl substituted

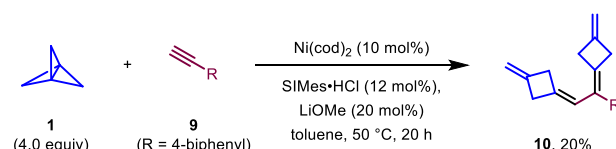
Scheme 3. Alkene scope^a



^a Reaction conditions: alkene (0.20 mmol), propellane (0.7–0.9 M in Et₂O, 4.0 equiv), Ni(cod)₂ (10 mol%), SIMes·HCl (12 mol%), LiOMe (20 mol%), and toluene (3 mL) at 50 °C for 20 h. Yield are of isolated products. ^b Reaction performed at room temperature.

alkenes were tolerated, such as pyridine (**7n**), quinoline (**7o**), indole (**7p**), furan (**7q**), and benzothiophene (**7r**), undergoing cyclopropanation in good to excellent yields. In addition to alkenes with aromatic substituents, conjugated 1,3-diene and 1,3-enyne substrates were also tolerated. These substrates displayed higher reactivity and reactions proceeded efficiently at room temperature, delivering alkenyl or alkynyl-substituted spirocyclic products **7t–7x** in good yield and with complete regioselectivity for reaction at the terminal alkene. We also investigated the reaction of terminal alkynes with **1** (Scheme 4). Interestingly, 4-ethynylbiphenyl (**9**) reacted via a carbene/alkyne metathesis rather than the expected cyclopropanation,²⁹ giving bis(3-methylenecyclobutylidene) product **10** in 20% yield.

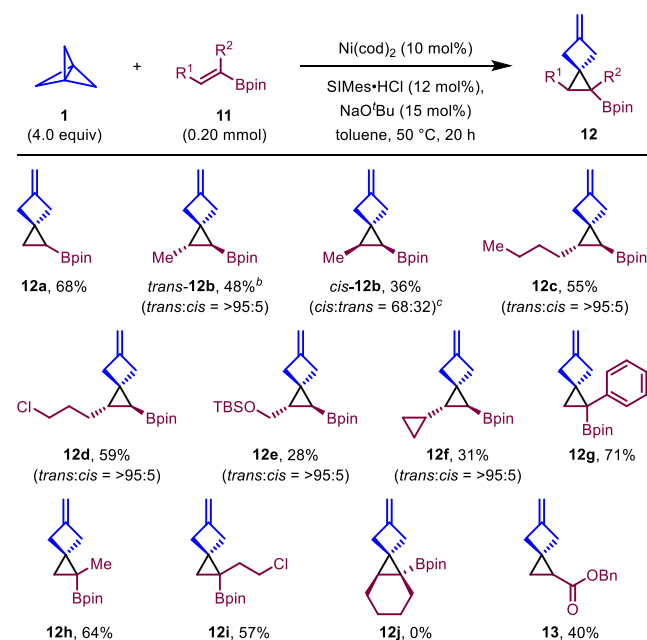
Scheme 4. Reaction of terminal alkynes



The presence of a conjugated π -system on the alkene substrate was found to be crucial for productive cyclopropanation, as alkyl-substituted alkenes (e.g., allylbenzene) were unreactive under our optimized conditions. Unfortunately, the cyclopropanation reaction also failed for α - and β -substituted styrenes. Therefore, we sought alternative alkene substrates that would undergo cyclopropanation while providing a synthetic handle that would allow subsequent substitution reactions. Boronic esters are highly versatile

moieties that can readily be transformed into a diverse array of functional groups.³⁰ Thus, we examined the nickel-catalyzed cyclopropanation reaction with alkenylboronic esters **11** (Scheme 5).³¹ We were pleased to find that vinylboronic acid pinacol ester underwent productive reaction, providing borylated methylenespiro[2.3]hexane **12a** in good yield.³² Furthermore, in contrast to the styrene derivatives, alkenylboronic esters with β -substitution were also suitable substrates. Various alkyl groups at the β -position were tolerated, providing products **12b–12f** in moderate to good yields and with excellent diastereoselectivity when *E*-alkene substrates were used. The stereospecificity of the reaction was examined by using (*Z*)-1-propenylboronic acid pinacol ester, which selectively provided the *syn* diastereomer of **12b** but only with a modest 32:68 *trans/cis* ratio (see below for further discussion). In addition to β -substitution, α -substituted alkenylboronic esters were efficiently cyclopropanated, providing tertiary benzylic (**12g**) and tertiary non-benzylic (**12h** and **12i**) cyclopropylboronic esters in good yields. Unfortunately, trisubstituted alkenes proved unreactive, with 1-cyclohexenylboronic ester pinacol ester failing to yield tricyclic product **12j**. Finally, the use of benzyl acrylate provided cyclopropyl carboxylate ester **13** in 40% yield.

Scheme 5. Alkenylboronic ester scope^a

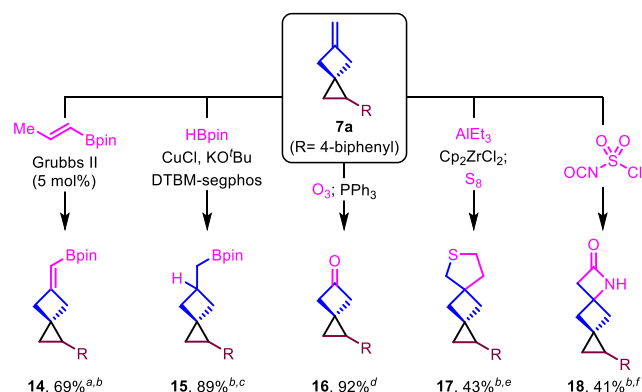


^a Yields are of isolated products. The *trans/cis* ratio was determined by GC/MS. ^b Using (*E*)-1-propenylboronic acid pinacol ester. ^c Using (*Z*)-1-propenylboronic acid pinacol ester

We next sought to highlight the synthetic utility of the methylenespiro[2.3]hexane skeleton (Scheme 6). Methylenecyclobutanes have previously found application in natural product total synthesis due to the versatility of the exocyclic alkene.³³ Thus, we used this moiety as a handle for diversification of cyclopropanation product **7a**. Transformation into synthetically useful organoboronic ester products was achieved via cross metathesis³⁴ and

hydroboration,³⁵ providing alkenylboronic ester **14** and alkylboronic ester **15**, respectively. Spiro[2.3]hexan-5-one derivative **16** could be prepared in excellent yield via ozonolysis. Finally, spirocyclic propagations were performed to access different sized heterocycles, including a carboalumination/thioetherification³⁶ to form tetrahydrothiophene **17**, and a [2+2] cycloaddition with chlorosulfonyl isocyanate to give β -lactam **18**.^{33c}

Scheme 6. Products derivatizations



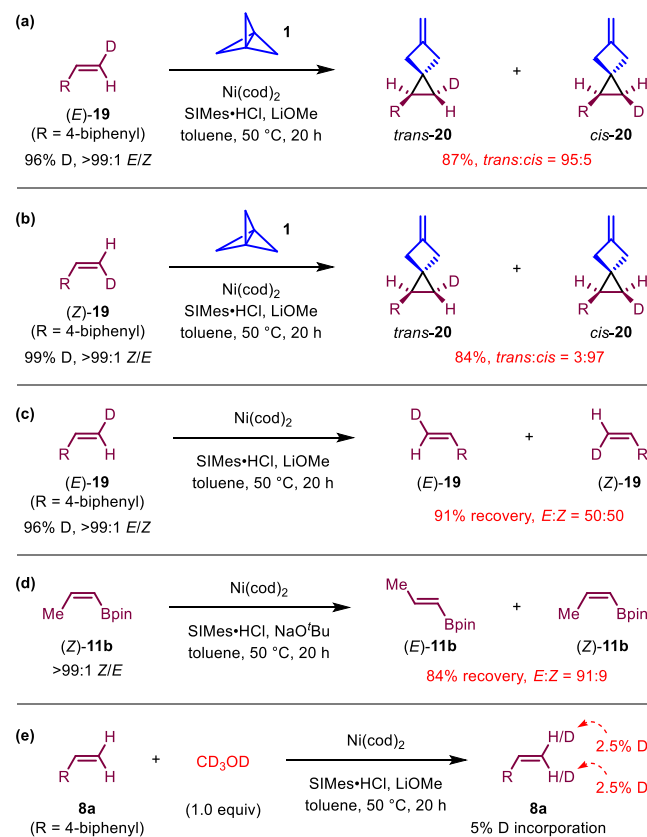
^a Prop-1-en-1-ylboronic acid pinacol ester, Grubbs 2nd generation catalyst (5 mol%), CH₂Cl₂, 50 °C. ^b Products formed in 52:48–56:44 d.r. ^c CuCl (5 mol%), DTBM-segphos (6 mol%), KO^tBu (20 mol%), HBpin (1.2 equiv), toluene, r.t. ^d O₃, MeOH/CH₂Cl₂, then PPh₃ (1.5 equiv). ^e Cp₂ZrCl₂ (5 mol%), Et₃Al (1.2 equiv), toluene, then sulfur (2.4 equiv). ^f Chlorosulfonyl isocyanate (1.0 equiv), Et₂O, r.t.

3. Mechanistic Studies

Our investigations into the mechanism of this nickel-catalyzed cyclopropanation initially focused on elucidating if the reaction proceeded via a single-electron pathway. This was considered due to the propensity of the bridgehead bond of **1** to react with free radicals³⁷ and because nickel-catalyzed reactions commonly involve single-electron transfer processes.²⁸ Furthermore, Wiberg has previously shown that **1** undergoes cyclopropanation reactions with highly activated electron-deficient π -systems and proposed that they proceed via a radical mechanism.^{26,38} In our nickel-catalyzed process, if a stepwise radical mechanism was operative, cyclopropanation of 1,2-disubstituted alkenes would be expected to proceed with poor stereocontrol, whereas two-electron pathways of a metal carbene intermediate (e.g., pathways A and B in Scheme 1) should be stereospecific. Therefore, we investigated the stereospecificity of the cyclopropanation reaction using both (*E*)- and (*Z*)- β -deutero-4-vinylbiphenyl (**19**) (Schemes 7a and 7b). Reaction of (*E*)-**19** (>99:1 *E/Z*) with **1** under the standard conditions afforded *trans*-**20** as the major product with a 95:5 ratio of isotopomers, while the reaction of (*Z*)-**19** (>99:1 *Z/E*) gave *cis*-**20** as the major product in a 97:3 ratio. The high stereoselectivity of these reactions support a stereoretentive cycloaddition of a nickel carbene rather than a radical pathway. We postulated that the small drop in selectivity in the reactions of (*E*)-**19** and (*Z*)-**19**, and the poor diastereoselectivity observed with (*Z*)-**11b** (see product *syn*-**12b**, Scheme 5), could be caused by isomerization of the

starting alkene prior to cyclopropanation. Indeed, submitting (*E*)-**19** and (*Z*)-**11b** to the standard reactions conditions but in the absence of **1** resulted in substantial isomerization, giving a 50:50 ratio of isomers of **19** and a 91:9 *E/Z* ratio for **11b** (Schemes 7c and 7d). In addition, when **8a** was treated with the nickel catalyst in the presence of methanol-*d*₄, approximately 5% deuterium incorporation was observed in the recovered alkene (Scheme 7e), which reveals the alkene isomerization stems from a nickel-hydride species generated from oxidative addition of Ni(0) to methanol.³⁹ Based on these experiments, we concluded that the cyclopropanation proceeds via a two-electron pathway involving reaction of the alkene substrate with a nickel carbene intermediate, as shown in Scheme 1.

Scheme 7. Mechanistic experiments



While metal carbenes have been proposed as intermediates in transition metal-catalyzed reactions of [1.1.1]propellane,²⁶ their mechanism of formation and subsequent reactivity has not been studied. Therefore, we used DFT (B3LYP-D3/6-311++G**//B3LYP-D3/6-311+G*; SMD, solvent = toluene, see Supporting Information for full details) to model the nickel catalytic cycle,⁴⁰ where the smaller NHC ligand **L** was used as a representative catalyst (Figure 1).^{41,42} Loss of a styrene from the 16-electron Ni(0) species **RS**, generating the 14-electron intermediate **I^A**, is an endergonic process, consistent with **RS** acting as an off-cycle resting state. With intermediate **I^A** + **1** + styrene defining the free-energy zero point of the cycle, coordination of propellane to **I^A** to give the Ni(0) intermediate **I^B** is thermodynamically favorable, with a ΔG of -8.3 kcal/mol. An alternative diradical ground state for the adduct

I^B (**I^{B*}**) was explored but was found to be too high in energy to be relevant (see Supporting Information for full details). The propellane adduct **I^B** then undergoes a concerted ring-opening where two C–C bonds are cleaved to generate the carbene intermediate **I^C** via transition state **TS^{BC}**. The subsequent cyclopropanation was found to proceed through a stepwise pathway (see pathway B, Scheme 1), with C–C bond formation, via transition state **TS^{CD}**, giving metallacyclobutane intermediate **I^D**. The regioselectivity of the formation of metallacyclobutane **I^D** favored C–Ni bond-formation at the benzylic carbon, as the alternative transition state **TS^{CD'}**, in which C–C bond-formation occurs at the benzylic carbon, is 3.5 kcal/mol higher in free energy than transition state **TS^{CD}**. Reductive elimination of the cyclopropane moiety, via **TS^{DE}**, then yields **I^E**, the Ni(0) adduct of the product, **7b**, which is in turn liberated by reaction with styrene, regenerating **I^A**.⁴³ It appears that π -coordination of the arene during the reductive elimination facilitates the process, a finding in accord with the experimental observation that replacing the arene with a more strongly coordinating alkene function allows the reaction temperature to be lowered (Scheme 3), whereas no reaction occurs when the coordinating group is removed (e.g., alkyl-substituted alkenes).

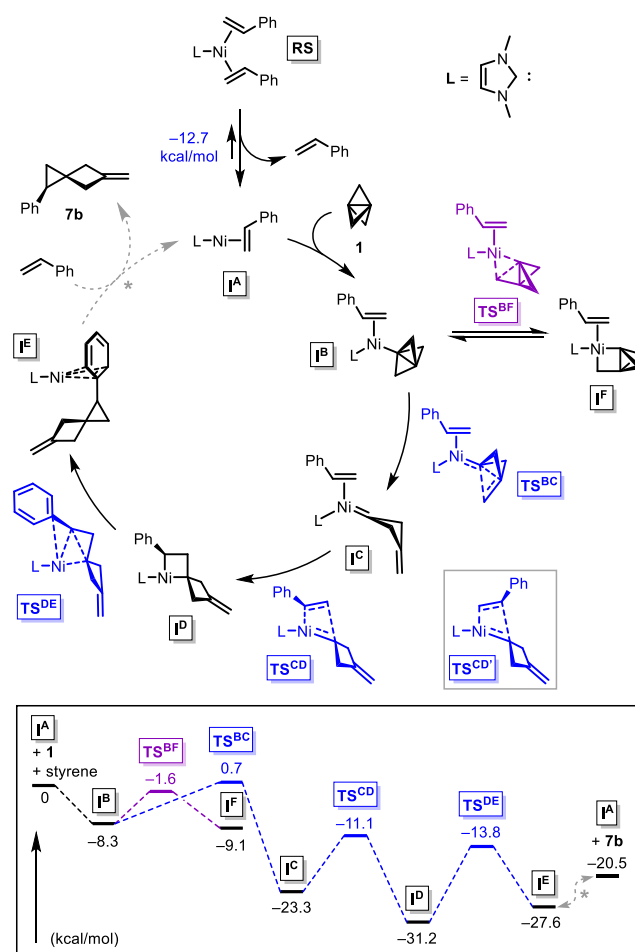


Figure 1. DFT-calculated catalytic cycle and associated free energy level diagram. *The individual ligand substitution steps (**I^E** to **I^A**) were not modelled.

Intermediate **I^B** can also undergo smooth, reversible oxidative addition to give an off-cycle metalla-[2.1.1]propellane intermediate **I^F**, a process calculated to be thermodynamically and kinetically competitive with the concerted ring-opening to form **I^C** (Figure 1). While two alternative pathways for cyclopropanation that proceed via **I^F** may be envisaged, these were found to be energetically less likely, at least in our model system (see Supporting information for full details).

The calculated intermediate **I^B** represents a rare example of a coordinated [1.1.1]propellane,⁴⁴ while intermediate **I^F** can formally be considered as a metalla-[2.1.1]propellane. To the best of our knowledge, while rare examples of transition metal-based metalla-[1.1.1]propellanes are known,⁴⁵ [2.1.1]-analogues have not been reported. The nature of the ‘inverted’ C–C bonds of small ring propellanes has been the subject of much debate in the literature,^{20a,46} with recent *ab initio* valence bond calculations by Wu and co-workers revealing that the inverted bond has predominant ‘charge-shift’ bonding character with little or no diradical contribution.^{47,48} Accordingly, a closer examination of the electronic structures of intermediates **I^B** and **I^F** (geometry optimization at the B3LYP/6-311++G** level of theory) was of interest.

The calculated C–C bond length of the inverted bond of the propellane ligand in **I^B** of 1.600 Å is marginally longer than either that calculated for free propellane at the same level of theory (1.582 Å) or measured for a closely related derivative (1.579 Å),⁴⁹ but is significantly shorter than the bridgehead carbon distance in bicyclo[1.1.1]pentane (1.845 Å),⁵⁰ which is indicative of a C–C bonding interaction. The coordination of the propellane in **I^B** is offset from linear, with a calculated angle between the inverted C–C bond axis and the nickel center of 151°. Meanwhile, the calculated Ni–C bond length to the propellane ligand (2.042 Å) is longer than that of the Ni–C bond for the carbene ligand (1.935 Å). Figure 2 shows both the bonding molecular orbitals (MO) between the propellane ligand and a d-orbital on nickel – an orbital that also shows significant involvement of the NHC donor – and a summary of key topological data, calculated using the Atoms in Molecules (AIM) method,⁵¹ along with Wiberg Bond Indices (WBI) for key bonds in **I^B** and propellane. Comparing the data, it is clear that the inverted C–C bond of propellane remains largely intact on coordination. The positive value for the Laplacian, $\nabla^2\rho$, is atypical of covalent C–C bonds, which tend to return negative values, but is in line with the charge-shift description of propellane inverted bonds.⁴⁹

The intermediate **I^F** could be viewed as containing either a metalla-[2.1.1]propellane (form **A** in Figure 3) or, at the other extreme, a nickel carbene complex with an intramolecularly coordinated alkene moiety (form **B**). Indeed, as described in the introduction, metal carbene intermediates are ubiquitous in catalytic cyclopropanations. However, the calculated Ni–C_a bond length (1.968 Å) is too long for any significant carbenic character, indeed it is longer than the Ni–C(NHC) bond (1.926 Å), which is generally accepted to be a single bond with very little retro-donation. By comparison, structurally characterized Ni(II) carbene complexes without heteroatom functionality on the carbene carbon display Ni=C bond lengths in the range 1.844 – 1.906 Å,⁵² while the Ni–C bond lengths of the very limited number of nickelacyclobutanes reported are 1.927 – 1.956 Å.⁵³ Meanwhile, despite being marginally shorter than a

typical C–C single bond, C_b–C_c is significantly longer than a double bond, even one coordinated to Ni, as highlighted by the calculated C–C bond length of 1.361 Å for the coordinated styrene ligand in **I^F**. Taken together, these bond metrics favor the metalla-[2.1.1]propellane form **A**, which would be expected to have an inverted C_a–C_b bond. Indeed, the separation of these carbon atoms is very similar to that calculated for [2.1.1]propellane at the same level of theory (Figure 3). An NBO analysis shows a σ -symmetry bonding orbital located between C_a and C_b while the equivalent MO has further density associated with the metal–C_c fragment. The WBI of the C_a–C_b bond clearly indicate a bonding interaction, however, an AIM analysis does not identify a bond critical point (bcp) between these two carbon atoms. This is perhaps not surprising in view of the extended nature of the MO, and the observation that organometallic ligands with such conjugation to metal centers do not always reveal bcp’s.⁵⁴ In contrast, the delocalization index ($\delta(\text{AB})$) for this interaction, also obtained from the AIM calculation, is clearly indicative of significant bonding.

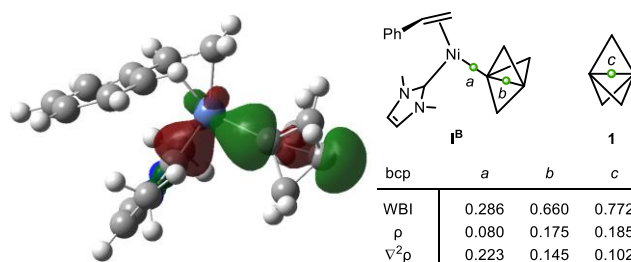


Figure 2. MO of the Ni-propellane σ -bond of intermediate **I^B** (isovalue = 0.05 (electron/bohr³)^{1/2}); AIM-calculated bond critical points (bcp, small green spheres), associated electron density (ρ) and Laplacian ($\nabla^2\rho$) values at the bcp's and Wiberg Bond Indices (WBI) of the bonds.

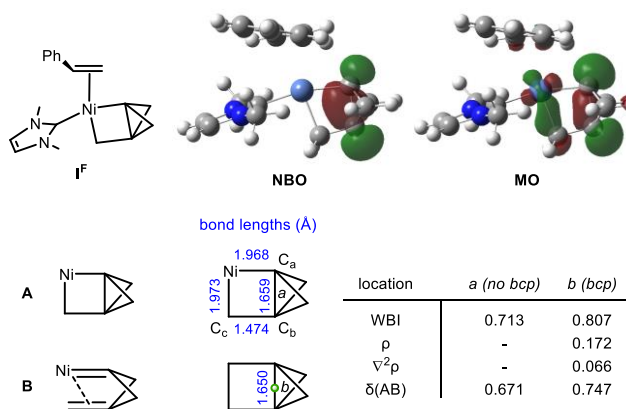


Figure 3. NBO and MO associated with the inverted C–C bond of intermediate **I^F** (isovalue = 0.05 (electron/bohr³)^{1/2}); WBI and AIM-calculated metrics (as defined in Figure 2) as well as AIM-derived delocalisation index ($\delta(\text{AB})$) values.

4. Conclusions

We have developed a new approach to methylenespiro[2.3]hexane derivatives via a nickel-catalyzed cyclopropanation of alkenes with [1.1.1]propellane. The

reaction involves a rare example of double C–C bond activation of [1.1.1]propellane to provide a methylenecyclobutylidene-metal intermediate. Nickel catalysis proved essential in preventing deleterious side reactions of the metal-carbene and enabled the successful application of a wide range of alkene substrates, including styrenes, 1,3-dienes, 1,3-ynes, and alkenyl boronic esters. The formation of a nickel carbene was supported both experimentally, by the high stereospecificity of the cyclopropanation of 1,2-disubstituted alkenes; and computationally, with DFT calculations showing the carbene is formed via a concerted double C–C bond cleavage of a nickel-[1.1.1]propellane complex. Given that transformations of propellane are dominated by additions across the bridgehead σ -bond to form bicyclo[1.1.1]pentanes, this nickel-catalyzed process unveils a new reaction mode that will enhance the application of [1.1.1]propellane in the synthesis of complex molecules.

ASSOCIATED CONTENT

Supporting Information.

Experimental procedures, full characterization data for new compounds, and details of computational studies are supplied in the Supporting Information. This material is available free of charge via the Internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

Corresponding Author

* r.bedford@bristol.ac.uk

* v.aggarwal@bristol.ac.uk

Notes

The authors declare no competing financial interests.

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